

REMARKS

Claims 1-48 were pending in the present application and claims 1-22 are under consideration. By virtue of this response, claims 24-48 have been canceled, claims 1-3 and 17-19 have been amended, and new claims 49-68 have been added. Accordingly, claims 1-22 and 49-68 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

The amendments to the claims find support in the specification. The amendment to claim 1 finds support, *inter alia*, in original claim 3. The amendments to claims 2 and 3 find support, *inter alia*, at page 13, lines 1-3 of the specification. Support for the amendment to claim 17 is replete in the specification (e.g. the Examples) and in the recitation of the term "sequence tagged site" in original claim 17. Support for the amendments to claims 18 and 19 and for new claims 49 and 68 is replete in the specification (see, e.g., Examples 1 and 2). New claims 50-59 and 60-67, depending from new claim 49, correspond to claims 2-11 and 14-21, respectively, and are supported by the original claims and/or in the specification as described *supra*.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

I. Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-22 were rejected under 35 U.S.C. § 112, first paragraph. The Office asserted the specification does not enable the reader to identify probes with a defined chromosomal location and does not provide hybridization conditions for probes.

Applicants respectfully disagree. Preparation and use of the claimed arrays is well within the skill of a scientist guided by the specification. One of ordinary skill guided by the specification would have no difficulty identifying sequences with a known chromosomal location (e.g., location of a gene on a particular chromosome or a particular chromosomal locus).

At the time the application was filed such information was readily available, and additional information has become available since filing. The specification clearly describes the use of public databases such as GenBank, EMBL, DDBJ, PDB, SWISS-PROT, EST, STS, GSS, and HTGS which include this information. For example, an exemplary STS database is referred to at page 31 of the specification. It is well established that a patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The specification provides ample guidance concerning the claimed arrays (see, e.g., page 7, lines 15-18, and page 11, line 24 to page 13, line 6).

In the case of claim 18, the Office asserts (1) that the specification does not provide a defined chromosomal location for the probes defined by the recited primer pairs and (2) the probes defined by these primer pairs "are useless without defining some chromosomal location and/or possible linkage to a genetic disease locus." As to (1), in addition to the ready availability of information about the STSs defined by these primer pairs from the sources discussed above, Table 1 additionally provides STS names and accession numbers for the primer pairs. One of skill would have no difficulty obtaining information about these STSs or their corresponding genes. As to (2), Applicants do not agree that chromosomal location and/or possible linkage to a genetic disease locus is required for the utility of the arrays. For example, the arrays can be used to screen for differential gene expression among multiple subjects (see, e.g., Abstract, specification at page 5, lines 1-14).

Finally, the Office acknowledges that a variety of hybridization conditions are discussed in the specification, but asserts that the use of the claimed arrays is not enabled because specific hybridization conditions for each probe are not taught, i.e., because "each probe sequence is generally different which required different hybridization conditions for the same stringency." Applicants respectfully disagree. If each probe required a different hybridization condition, array technology itself would be impractical, which is clearly not the case. Applicants submit that, provided with the guidance of the specification and knowledge in the art, it is well within

the ability of the skilled practitioner to use the arrays of the invention with no undue experimentation. Applicants note that with regard to hybridization technology, the level of skill in the art is high and the physical parameters of hybridization are fairly well known and predictable. This invention can be made and used without undue experimentation.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 18-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 has been amended to increase clarity.

Claim 19 has been amended to increase clarity by noting that the target-probe complex is formed by hybridization. The hybridization complex can, of course, be stabilized by chemical cross-linking and other means.

III. Rejections under 35 U.S.C. § 103(a)

Claims 1-7, 9-17, and 19-22 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable in view of Duggan et al. *Nat. Genetics* 21 (Suppl.):10(1999) in view of Schena et al., *Science* 270:467 (1995), taken further in view of Wilcox et al., *Nuc. Acids Res.* 19:1837 (1991). Claims 1-17 and 19-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Duggan et al., Schena et al., and Wilcox et al., and in view of Fodor et al. (Pat. 5,510,270). Applicants respectfully traverse.

The Cited Art

1. Duggan et al.

Duggan et al. reviews the making and use of microarrays of cDNA probes. The Office notes that Duggan et al. describes formulating microarrays with polynucleotides of from 600 to 2400 bases in length. The Office stated that this range is "deemed to overlap with the

range of 50 to about 500" nucleotides as recited in claim 1. Duggan et al. notes arrays may include cDNAs that contain 3' untranslated sequences.

2. Schena et al.

Schena et al. describes expression profiles using cDNA arrays. Specifically, Schena et al. described microarrays prepared by high-speed robotic printing of *Arabidopsis* cDNAs on glass, and are used for quantitative monitoring of gene expression patterns. The cDNAs of the array described by Schena et al. averaged 1.0 kb in length and included "14 complete sequences" and "31 ESTs." The Office notes that the labeled polynucleotides used by Schena et al. to probe the immobilized cDNAs included 3' sequences¹

3. Fodor

Fodor is cited as describing arrays in which immobilized "probes" are localized in a predetermined region having the dimensions recited in instant claim 8.

4. Wilcox et al.

Wilcox et al. described a mapping strategy in which primer pairs defining gene-specific sequence-tagged sites (STSs) are used to amplify human sequences in panels of human-hamster somatic cell hybrids, thereby assigning the STSs to specific chromosomes or chromosome regions. Wilcox et al. does not teach or suggest arrays. Wilcox et al. is relied on by the Office to show the presence of 3'-untranslated sequences in cDNAs made by "oligo(A) primed synthesis."²

¹ It appears the Office may have incorrectly equated the labeled hybridization probes described in footnote 5 of Schena et al. and the immobilized probes of the instant invention (see page 7, lines 1-5 of the Office Action). Although the term "probes" is used in both cases, the immobilized probes of the invention and labeled probes of Schena et al. (representing heterogeneous transcripts derived from total RNA) are entirely different.

² It is understood by the Applicants that "oligo dT" primed synthesis is intended.

The Traverse

The Office asserts that it would have been obvious to “practice the arrays of Duggan et al. as further detailed in Schena et al., with poly(A) primed probes which contain 3’ untranslated regions of transcripts as verified in Wilcox et al. thus resulting in the practice of the instant invention.”

Applicants respectfully maintain that no *prima facie* case of obviousness has been established by the Office. To establish *prima facie* obviousness, the Office must indicate where the prior art provides reason or motivation for one of skill to make the claimed composition or carry out the claimed method. The Office must also demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting to make the composition or carry out the method. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). In determining obviousness the reference must be read without benefit of applicants’ teachings.

The basis for the rejection of claims set forth by the Office is it allegedly would have been obvious to “practice the arrays of Duggan et al. as further detailed in Schena et al, with poly(A) primed probes which contain the 3’-untranslated region of transcripts.” In articulating the rejection, the Office noted “the instant probes are not limited to being ‘only’ targeted to the 3’ untranslated section of the target transcripts.”

First, the alleged relevance of Duggan et al. was based, at least in part, on the assertion by the Office that the size range of “from 600 to 2400 bases in length” was deemed to overlap the range of “about 50 to about 500” nucleotides as was recited in claim 1. For clarity of the record, the Office is respectfully asked to explain why two nonoverlapping ranges are deemed to overlap. The amendment of claim 1 to recite a range of about 50 to 500 nucleotides clearly overcomes this basis for the rejection, as does the recitation in amended claims 2 and 3 of even shorter probes. Nothing in Duggan et al., alone or in combination with the other cited references, suggested an array of short probes complementary to the 3’ untranslated sequences of gene transcripts. At best, Duggan et al. described that long cDNA probes on arrays may incidentally include 3’ untranslated regions along with coding regions.

Thus, nothing in the Duggan reference taught or suggested the present invention.

The Office stated “It is noted that the instant probes are not limited to being ‘only’ targeted to the 3’ untranslated section of the target transcripts.” Applicants maintain that the

selection of short probes complementary to the 3' untranslated sequences of gene transcripts, and the recitation that the arrays comprise at least 100 such probes renders the claimed arrays nonobvious. Further, new claims 49 and 68 recite that each polynucleotide probe of the plurality (comprising at least 100 polynucleotides that are each complementary to a distinct gene transcript) is complementary to only the 3' untranslated sequence of a gene transcript, specifically addressing the concerns of the Office. It is noted that the Schena et al. article cited in Duggan and relied on by the Office teaches that full-length cDNAs should be used as probes and, further, all of the ESTs cited by Schena et al. for which a GenBank alignment to cDNA is available (i.e., all ESTs except one³) included protein coding sequences and were not limited to 3' untranslated sequences.

In summary, nothing in the cited references taught or suggested the present invention. Applicants respectfully request that this rejection be withdrawn.

IV. Objections and Other Matters

A. Title

The Office states that a new title is required that is clearly indicative of the invention to which the claims are directed. Applicants wish to defer any amendment of the title until they have received an indication that claims are allowable, thereby permitting the most appropriate title to be selected.

B. "Embedded hyperlink"

Applicants do not intend the web addresses on pages 12 and 31 to be active hyperlinks. They are citations to databases. To the extent that the recitation of a web sites at page 12 and page 31 are considered by the Office to be "embedded hyperlinks," Applicants refer to MPEP 608.01, which states, in part "[When] applicant does not intend to have these hyperlinks be active links, examiners should not object to these hyperlinks. The Office will disable these hyperlinks when preparing the text to be loaded onto the USPTO web database."

³ Applicants did not find a cDNA corresponding to the Schena et al. EST83 in Genbank.

C. Footnotes

The Office states objected to the footnotes on pages 12 and 13. The specification has been amended to incorporate the footnotes into the body of the specification.

D. Replacement pages

The Office requested replacement pages for pages 32-35. These pages are enclosed. No new matter is added.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 421452000100.

Respectfully submitted,

Dated: June 28, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 12, lines 2-4, please delete [Non-limiting examples of these programs are Blast¹, Fasta², DNA Star, MegAlign, and GeneJockey.] and the accompanying footnotes, and insert in its place --Non-limiting examples of these programs are Blast (available on the worldwide web at <http://www.ncbi.nlm.nih.gov/BLAST/>), Fasta (Genetics Computing Group package, Madison, Wisconsin), DNA Star, MegAlign, and GeneJockey.--

In the Claims:

Please cancel claims 24-48.

Please amend claims 1, 2, 3, 17, 18 and 19 as follows:

1. (Amended) An array comprising a plurality of polynucleotide probes immobilized on a solid support, wherein:
 - (a) the plurality of polynucleotide probes corresponds to a multiplicity of gene transcripts and comprises at least 100 polynucleotides that are each complementary to a distinct gene transcript;
 - (b) each polynucleotide probe of the plurality is localized to a predetermined region on the solid support;
 - (c) each polynucleotide probe of the plurality is from about 50 to [about] 500 nucleotides in length;
 - (d) each polynucleotide probe of the plurality is complementary to 3' untranslated sequence of a gene transcript, said untranslated sequence having a defined chromosomal location.
2. (Amended) An array of claim 1, wherein each polynucleotide probe of the plurality of polynucleotide probes is from about 50 to 400 nucleotides in length [comprises at least about 20 polynucleotides, each being complementary to a distinct gene transcript].

3. (Amended) An array of claim 1, wherein each polynucleotide probe of the plurality of polynucleotide probes is from about 50 to 300 nucleotides in length [comprises at least about 100 polynucleotides, each being complementary to a distinct gene transcript].

17. (Amended) An array of claim 1, [where the] wherein each polynucleotide probe of the plurality [of polynucleotide probe comprises sequence-tagged site (STS) tages] is prepared by amplification of genomic DNA or cDNA using a pair of primers that amplify the region corresponding to 3' untranslated sequence of a gene transcript.

18. (Amended) An array of claim 1, wherein [each] the array comprises a polynucleotide probe prepared by amplification of genomic DNA or cDNA [is amplified] using a primer pair selected from the group consisting of SEQ ID NOS. 1-2, 3-4, 5-6, 7-8, 9-10, 11-12, 13-14, 15-16, 17-18, 19-20, 21-22, 23-24, 25-26, 27-28, 29-30, 31-32, 33-34, 35-36, 37-38, 39-40, 41-42, 43-44, 45-46, 47-48, 49-50, 51-52, 53-54, 55-56, 57-58, 59-60, 61-62, 63-64, 65-66, and 67-68.

19. (Amended) An array of claim 1 further comprising target polynucleotides corresponding to gene transcripts expressed in a subject, wherein the target polynucleotides are bound to the polynucleotide probes in form of stable target-probe hybridization complexes.

Please add new claims 49-68.